REVIEW ARTICLE

Expert Opinion by Clinicians on the Use of Insulin Therapy in People with Hepatic Impairment

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Abstract

People with type 2 diabetes mellitus (T2DM) have a higher risk of developing chronic liver disease (CLD) and its complications. T2DM, obesity, and insulin resistance are all strongly associated with nonalcoholic fatty liver disease (NAFLD). Conversely, people suffering from cirrhosis have reduced glucose tolerance in approximately 60% of cases, diabetes in 20% of cases, and insulin-mediated glucose clearance is lowered by 50% as compared with those who do not have cirrhosis. An exploratory review was conducted using existing published evidence from clinical studies on dosing and titrations of individual insulin formulations in people with CLD to optimize insulin dosage titration for minimizing hypoglycemia risk.

This article discusses current hyperglycemia treatment techniques for patients with CLD as well as the consensus recommendations on insulin use in special populations with T2DM and hepatic impairment. Based on available evidence and expert diabetologists' recommendations, careful insulin dose titration, customized glycemic targets, and frequent glucose screening are recommended for optimal glycemic management without hypoglycemia in CLD. Long-acting insulin should be avoided or used when short-acting insulin fails to provide adequate glycemic control with raised fasting blood sugar levels. While the patient's glucose profile is being evaluated, the prandial insulin dose can be lowered by 25% initially. The dose can be titrated based on the patient's postprandial glycemic expression and whether their food intake meets the Child–Pugh scores A and B categories. Titrating premixed insulins is difficult for patients in class C since their appetite and overall health are constantly compromised and in flux.

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Introduction

Chronic Liver Disease

As the 10th leading cause of morbidity and mortality worldwide, it is evident that CLD eventually leads to cirrhosis and/or liver cancer, a serious public health concern.[1] Viral hepatitis [chronic hepatitis B virus (HBV) and hepatitis C virus (HCV)], NAFLD, and alcoholic liver disease are the main causes of CLD.[1] The data from the Global Burden of Disease study (between 2012 and 2017) indicated that liver disease claims 2.14 million lives each year and liver disease-related fatalities have increased by 11.4% (16.0% increase in liver cancer deaths and 8.7% increase in cirrhosis deaths).[1] A meta-analysis by Younossi et al. estimated that the global prevalence of metabolic comorbidities associated with NAFLD included obesity (51.34%), T2DM (22.51%), hyperlipidemia (69.16%), hypertension (39.34%), and metabolic syndrome (42.54%).[2] The NAFLD prevalence has increased along with rising global trends in obesity, T2DM, and metabolic syndrome.[2,3]

Diabetes

According to the International Diabetes Federation, Diabetes Atlas 2021 (10th edition), 537 million adults (20–79 years) have diabetes and three out of four people with diabetes reside in low- and middle-income countries.[4] Diabetes affected 90 million people (1 in 11) in Southeast Asia in the year 2021, which is expected to rise to 113 million by 2030.[4] Diabetes was associated with 6.7 million fatalities worldwide in 2021, that is, one death every 5 seconds, with 747,000 deaths in Southeast Asia.[4]

Diabetes—A Risk Factor in People with Hepatic Impairment

Diabetes and CLD have a well-established relationship. According to existing literature, people with T2DM are significantly more likely than the general population to progress to advanced CLD and experience related complications, such as abnormal liver enzymes, NAFLD, cirrhosis, hepatocellular cancer, and acute liver failure.[3,5] Diabetes occurring as a complication of cirrhosis is known as hepatogenous diabetes, which can only be diagnosed after the onset of liver disease.[6]

Insulin resistance, obesity, and T2DM are all strongly associated with NAFLD.[7] Globally, NAFLD incidence and prevalence are increasing, imposing a huge clinical and economic burden, in addition to poor patient-reported outcomes.[3,8] Cirrhosis and diabetes have a contentious relationship with underlying insulin resistance being the main pathophysiological defect. People with cirrhosis showed impaired glucose tolerance in 60% of cases and diabetes in 20% of cases, as well as a 50% reduction in insulin-mediated glucose disposal.[5]

In people with diabetes, CLD-related mortality was seen to be increasing.[9] Kim et al. analyzed the National Vital Statistics System database to understand the trends in CLD-related mortality in people with diabetes (n = 48,761) in the United States alone and demonstrated that between 2007 and 2017, the mortality rate in people with NAFLD and acute liver disease increased by 11.6 and 1.4%, respectively.[9] The age-standardized prevalence of suspected fibrosis (15.7–24.6%) and suspected cirrhosis (8.5–11.4%) was highest among people with diabetes and prediabetes in the 2017–2018 National Health and Nutrition Examination Survey, which included 4207 people with normal glucose, prediabetes [glycated hemoglobin (HbA1c) = 5.7–6.4%], and diabetes (HbA1c = 6.5%).[10] Thus, it has been recommended that people with diabetes should be screened for NAFLD and NAFLD-related fibrosis.[10]

Glycogen deposition, steatosis, NASH, fibrosis, cirrhosis, biliary disease, cholelithiasis,

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cholecystitis, and complications of diabetes medication are part of the spectrum of liver diseases that occur because of diabetes mellitus (cholestatic and necro-inflammatory liver disease).[11]

New-onset Diabetes after Transplantation (NODAT)

One of the clinically important complications of solid organ transplantation (particularly liver, kidney, or heart recipients) is the development of NODAT or post-transplantation diabetes mellitus (PTDM),[12] which is mainly associated with metabolic disorders and considerably affects the quality of life and increases mortality.[13,14] The incidence of NODAT varies depending upon the criteria used to diagnose diabetes after transplantation. PTDM affects 20–40% of liver transplant recipients and 10–20% of kidney transplant recipients.[15] The risk factors for developing NODAT or post-liver transplantation diabetes mellitus (PLTDM) and diabetes are similar, and also influenced by the administration of specific drugs following organ transplantation.[12–14] The diagnosis of NODAT/PLTDM also depends on the need for insulin/antidiabetic drugs 1 month after liver transplant.[12]

Based on published evidence from clinical trials, an exploratory review-analysis was undertaken on the dosage and titration of various insulin preparations in people with CLD, with some focus on newer insulin analogs because of their unaltered pharmacokinetics (PK) and low risk of hypoglycemia in CLD situations. Thus, this article summarizes the current therapies for managing hyperglycemia in people with CLD as well as consensus on recommendations on insulin use in special populations with T2DM and hepatic impairment.

Association of Diabetes with Liver Disease

The onset of diabetes in cirrhotic patients signals the progression of their disease and may even possibly cause liver failure.[11] Diabetes management in people with CLD (or cirrhosis) can be challenging particularly those with Child–Pugh class C score, and these individuals should be differentiated from those without CLD by distinguishing characteristics.[6,16,17]

Altered Drug Metabolism including Oral Antidiabetic Drugs (OADs) in the Liver

Chronic liver disease is marked by a variety of metabolic changes, the majority of which are catabolic.[18] The metabolism of certain drugs may be noticeably affected in liver disease.[19] Hepatic blood flow may be impaired in disease states and may impact the activity of drug-metabolizing enzymes and plasma protein production.[17,19,20] Liver disease does affect the PK of certain drugs, notably those metabolized by the cytochromes P450 enzyme system, necessitating dosage adjustments or titration.[17,20]

Reduced gluconeogenesis ability, resulting in lower hepatic glucose output and decreased hepatic insulin breakdown, may minimize the requirement in people with decompensated liver disease. In contrast, people with impaired hepatic function may require more insulin to compensate for their insulin resistance.[7]

Cirrhosis has been associated with severe peripheral hyperinsulinism,[21] which was caused by a higher rate of insulin secretion as well as a significant reduction in insulin hepatic clearance. Insulin uptake in the cirrhotic liver was investigated by Nygren et al. in six people with alcoholic liver cirrhosis (Laennec's cirrhosis) and 10 people (control) with other conditions.[22] They discovered that the average hepatic insulin uptake was 13.5%, which was significantly lower ($p < 0.001$) than in the control group (51.5%). This conclusion implies that the cirrhotic liver takes less insulin from portal blood than the noncirrhotic liver, and it supports the findings of other researchers who estimated hepatic insulin uptake using the relationship between insulin and C-peptide in peripheral venous blood.[22] A case study in four patients with cirrhosis and poorly controlled T2DM suggested that the continuous subcutaneous insulin infusion helped regulate blood glucose levels in these patients and to reduce the daily dose of insulin.[23]

The therapy of T2DM in cirrhosis individuals is difficult due to the need for precise adjustment based on the extent of liver function impairment, as well as a lack of a summary of the limited data available.[24] Many antidiabetic agents are contraindicated or must be used with caution in those with liver disease.[7] Due to reduced liver metabolism and longer drug half-life, some OADs may cause cholestatic jaundice and severe hypoglycemia.[16]

Glucose Intolerance, Insulin Resistance, and Hypoglycemia

Chronic liver disease is often associated with glucose intolerance (especially after an oral glucose load) and increased insulin resistance, affecting endogenous glucose production, oxidative and nonoxidative glucose disposal, lipolysis, and lipid oxidation.[17,18,25] Glucose intolerance affects 60–80% of people with liver disease, and nearly 20% develop diabetes.[11,26]

Beta-blocker therapy has beneficial effects in patients with cirrhosis, mainly to prevent variceal hemorrhage.[27] Use of nonselective beta-blockers such as propanol may seriously impair glucose recovery from insulin-mediated hypoglycemia.[27]

The cause of insulin resistance, which leads to impaired glucose tolerance or diabetes mellitus, remains uncertain.[18] The existence of liver disease (unless it is decompensated) has a limited effect on the management of diabetes. Hypoglycemia should be regularly monitored in people with decompensated liver disease.[7]

Cirrhosis and HCV infection doubles the risk of T2DM compared to HBV infection.[25] HCV infection triggers glucose intolerance in people with cirrhosis.[25] Insulin resistance has been associated with the presence of serum HCV core, the severity of hepatic fibrosis, and decreased expression of hepatic insulin receptor substrates in people with HCV infection.[25]

Defective glucose storage can lead to malnutrition in people with CLD.[18] Lifestyle modification can be recommended in people with mild/moderate hyperglycemia and compensated liver disease; however, stringent dietary restrictions should be avoided at all costs because it could lead to malnutrition.[16]

Lactic Acidosis in Decompensated Liver Disease

In cirrhosis, sepsis, hemorrhage, or hypoperfusion, increased lactate production due to poor utilization and hepatic metabolism can lead to lactate accumulation and clinically severe lactic acidosis (serum lactic acid ≥5 mmol/L; normal lactate concentration = 2.0 mmol/L).[17,26,28] Metformin is not recommended for people with hepatic insufficiency since it increases the risk of lactic acidosis.[28]

Acidosis has several effects on insulin sensitivity and resistance. High doses of insulin and dextrose treatment can worsen lactic acidosis, according to one case study in a patient (18-year-old female) with Mauriac syndrome (glycogenic hepatopathy with poorly managed diabetes mellitus).[29]

Malnutrition

The severity of malnutrition has been associated with the progression of liver disease.[30] Since the liver is involved in nutritional metabolism, energy balance, and many other physiological functions, malnutrition is a well-known consequence of CLD reported in 65–90% in different studies.[17,30,31] Malnutrition has a significant impact on patient outcomes and is among the most significant prognostic variables in liver cirrhosis.[30,31] Malnutrition in liver disease can be caused by reduced dietary/nutrient intake, alterations in drug metabolism, and drug-induced malnutrition.[31]

Hypokalemia, hypomagnesemia, hypophosphatemia, and hypoglycemia are

the most common and possibly lifethreatening anomalies observed in individuals with acute liver failure. Protein restriction may worsen hepatic encephalopathy by increasing endogenous protein catabolism, whereas a higher protein intake appears to protect against problems such as hepatic encephalopathy.[31] Severe hypoalbuminemia and ascites are common in people with severe hepatic dysfunction.[17,32]

Butt et al. found a statistically significant ($p < 0.05$) association between nutritional status and the Child–Pugh stage of hepatic cirrhosis.[30] People in Child–Pugh class C showed significantly lower mean values of body mass index (BMI), triceps skin-old thickness, mid-arm muscle circumference, serum albumin, average daily food intake, and prolonged prothrombin time.[30]

There is currently no standardized treatment or evidence-based nutritional interventions for malnutrition that can be used to reduce malnutrition in people with CLD and acute liver failure and hence improve their prognosis.[31] About half of the population with T2DM and CLD are malnourished; lifestyle adjustments (diet, weight loss, exercises, abstaining from alcohol) may help in improving overall health.[7]

Insulin and insulin analogs are the only effective and safest therapy options available in persons with T2DM and CLD if OADs, lifestyle, and diet interventions are insufficient; nonetheless, people should be warned about signs of hypoglycemia.[7]

Insulin Requirement

Many clinicians are cautious to prescribe OADs, especially metformin, to people with T2DM and CLD.[16] Incretin-based treatments, such as DPP-4 inhibitors and GLP-1 receptor agonists, are promising choices for treating NAFLD/NASH, however, there is insufficient evidence from a major clinical trial.[16]

Since its discovery and early clinical use in the 1920s, insulin therapy has transformed the treatment of both T1DM and T2DM. Following that, many types of insulin were developed, ranging from human insulin (HI) to analog insulin, rapid-acting insulin to long-acting insulin.[33] Insulin requirement depends on whether there is a reduction in gluconeogenesis or insulin resistance.[16]

Recommendations and Dose Modification of Insulin in Hepatic Impairment

A multidisciplinary approach and expert opinion for glycemic targets and dose modifications of different antidiabetic agents may help people with diabetes and CLD maintain a good quality of care or life.[7,17] Diabetes treatment centers should include a liver examination for staging and treatment of individuals with NAFLD, NASH, or cirrhosis.[3] A rise in NAFLD awareness among health care professionals and caregivers of individuals with diabetes could help identify patients at risk of liver fibrosis/cirrhosis and prevent complications.[3]

To treat hyperglycemia, most diabetic patients, including those with liver cirrhosis, need to take oral diabetes medications and/or insulin.[34] A systematic review conducted by Tang et al. compared the efficacy of antidiabetic agents (ADAs) on NAFLD in patients with T2DM. The study showed evidence that the combination therapy with insulin/metformin for 3–7 months improved hepatic fat content.[35] There are other oral agents like pioglitazone, SGLT2i, and GLP1-RA that have shown benefits in NAFLD in those with diabetes.[35] Further discussion on oral agents is beyond the scope of this review.

Although clinical studies on insulin-treated people with diabetes having CLD are limited, insulin therapy can be administered at any stage of hepatic impairment.[7] Progressive breakthroughs in the techniques for protraction or prolongation of insulin activity have spurred the growth of basal insulin therapy to establish this desired profile in patients.[36] Insulin should be initiated if the patients do not respond to OADs alone or in combination, or if they have hepatic failure.[37] When the blood glucose levels are >180 mg/dL or in critically ill people, basal or short-acting insulins could be used to overcome glucose fluctuations and improve glycemic levels.[38]

Insulin, preferably short-acting insulins, is the first-line treatment for diabetes in people with liver diseases such as cirrhosis or chronic hepatitis[11] and chronic liver failure.[11,17] Short-term intensive insulin treatment is preferred for new-onset diabetes mellitus patients who have HbA1c >9% or in kidney transplant recipients.[39,40]

Basal insulin therapy has progressed over time from first-generation analogs (glargine U-100, detemir) to second-generation analogs (glargine U-300, degludec) to ultra-long-acting formulations (icodec).[36] The Research Society for the Study of Diabetes in India-Endocrine Society of India Consensus Group recommends the use of rapid-acting insulin analogs (insulin aspart or lispro) to attain targeted glycemic levels with a low risk of hypoglycemia in T2DM individuals with hepatic impairment.[38] When compared to neutral protamine Hagedorn insulin or premixed insulins, evidence suggests that basal insulin analogs such glargine, detemir, and degludec are effective and safe, with a lower risk of hypoglycemia and weight gain.[38]

The insulin dose should be titrated to the requirements to reduce the risk of hypoglycemia. Newer insulin analogs may be chosen as their PK is unaltered and possesses a low risk of hypoglycemia.[17] Insulin therapy is usually initiated with basal insulin added to OADs and then switched to either insulin alone as a twice-daily fixed mixture regimen or a basal-bolus regimen, depending on the individual's condition.[7]

Management of PTDM requires a multifaceted customized approach along with the step-wise approach recommended for T2DM.[41] In patients with PTDM, the choice between insulin and OADs depends on many factors including the severity of hyperglycemia.[40] In cases of early posttransplant period or life-threatening emergencies, intravenous insulin should be administered to stabilize the patient's condition before switching to subcutaneous insulin or OADs.[15,41] *Insulin (alone or in combination with OADs) continues to be the treatment of choice in the hospital setting for managing hyperglycemia, PTDM, and preexisting diabetes/diabetes.*[12,40–42] Patients with poor glycemic control can continue insulin after discharge from the hospital with frequent self-monitoring of blood glucose (SMBG) to titrate insulin doses and to determine if it can be switched to OADs if glucose levels are achieved.[12,42]

Individualized insulin therapy is desirable based on the risk of hypoglycemia, comorbid conditions, functionality, costing, and in special populations.[38]

The next section discusses the evidence available for initiating insulin therapy in people with diabetes and CLD.

Available Evidence on Insulin Therapy in CLD

The prescribing information of selected insulin preparations (basal, prandial, and premixed insulins) for dose modification based on the PK/pharmacodynamic (PD) profile in hepatic impairment is presented in Table 1.

Basal Insulins

Insulin Detemir

Insulin detemir (Levemir®) can be used in hepatic impairment. The efficacy of insulin detemir was studied in two patients with significant hypertriglyceridemia and established NAFLD.[43]

Insulin detemir reversibly binds to serum albumin, making it hepatoselective insulin. The albumin–insulin molecule cannot pass through the capillary endothelial cell barrier to reach peripheral adipocytes, whereas the albumin–detemir molecule can freely pass

Table 1: Package insert recommendations for basal, prandial, and premix insulins in CLD

Generic name (company)	*Trade name*	*Use in hepatic insufficiency*	*Reference*
Insulin detemir (Novo Nordisk)	Levemir®	Careful glucose monitoring and dose adjustments of Levemir® may be necessary for patients with hepatic impairment	Levemir® (insulin detemir injection) for subcutaneous use. Novo Nordisk A/S. Revised Nov 2019. https://www.novo-pi.com/levemir.pdf
Insulin glargine (Sanofi)	Lantus®	Frequent glucose monitoring and dose adjustment may be necessary	Lantus® (insulin glargine injection) for subcutaneous use. Sanofi-aventis US LLC. Revised Dec 2020. https://products.sanofi.us/Lantus/lantus.pdf
Insulin degludec (Novo Nordisk)	Tresiba®	Careful glucose monitoring and dose adjustments of Tresiba® may be necessary for patients with hepatic impairment	Tresiba® (insulin degludec injection) for subcutaneous use. Novo Nordisk A/S. Revised Nov 2019. https://www.novo-pi.com/tresiba.pdf
Insulin aspart (Novo Nordisk)	NovoRapid®	Glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis	NovoRapid® (insulin aspart injection) for subcutaneous use. Novo Nordisk A/S. Revised Sep 2020. https://www.novo-pi.com/insulinaspart.pdf
Insulin lispro (Eli Lilly)	Humalog®	Patients with hepatic impairment may be at increased risk of hypoglycemia and may require a more frequent Humalog® dose adjustment and more frequent blood glucose monitoring	Humalog® (insulin glargine injection) for subcutaneous use. Lilly USA, LLC. Revised Apr 2020. https://uspl.lilly.com/humalog/humalog.html#pi
Insulin glulisine (Sanofi)	Apidra®	Patients with hepatic impairment may be at increased risk of hypoglycemia and may require a more frequent Apidra® dose adjustment and more frequent blood glucose monitoring	Apidra® (insulin glulisine injection) for subcutaneous or intravenous use. Sanofi-aventis US LLC. Revised Dec 2020. https://products.sanofi.us/apidra/apidra.html
Biphasic insulin aspart (Novo Nordisk)	NovoMix®	The PK has not been investigated in patients with hepatic impairment. Glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis	NovoMix® (biphasic insulin aspart injection) for subcutaneous use. Novo Nordisk A/S. Revised Nov 2020. https://www.ema.europa.eu/en/documents/product-information/novomix-epar-product-information_en.pdf
Biphasic insulin lispro (Eli Lilly)	Humalog® Mix 75/25	The effect of hepatic impairment on the pharmacokinetics of Humalog® Mix 75/25 has not been studied. Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent Humalog® Mix 75/25 dose adjustment and more frequent glucose monitoring	Humalog® Mix 75/25 (insulin lispro protamine and insulin lispro injectable suspension) for subcutaneous use. Lilly USA, LLC. Revised Apr 2020. https://uspl.lilly.com/humalog7525/humalog7525.html#pi
Coformulation of insulin degludec and insulin aspart (Novo Nordisk)	Ryzodeg®	Glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis	Ryzodeg® (insulin degludec/insulin aspart) solution for injection in pre-filled pen/cartridge.Novo Nordisk A/S. Revised Sep 2021. https://www.ema.europa.eu/en/documents/product-information/ryzodeg-epar-product-information_en.pdf https://www.ema.europa.eu/en/documents/product-information/novomix-epar-product-information_en.pdf

through the liver sinusoids. This allows it to have a higher impact on hepatocytes than on other tissues in the body.[43]

Less hepatic exposure to insulin may limit the efficacy of hepatoselective insulin in NAFLD. Several factors affecting hepatocytes cause hyperglycemia because insulin stimulates the liver to store glucose in the form of glycogen while also turning off gluconeogenesis.[43]

Insulin detemir is hepatoselective insulin with less efficacy in achieving glycemic control. It could be due to hyperglyceridemia, which could reduce the efficacy of detemir or the consequences of lipid infiltration into the hepatic parenchyma. Patients may need high insulin doses resulting in weight gain.[43]

Insulin Degludec

In comparison to insulin glargine, insulin degludec is a new generation ultra-long basal insulin that allows for slow and continuous absorption, resulting in a flat action profile and four times lesser glycemic variability.[44] Because of the longer duration of action (>42 hours), once-daily dose scheduling becomes even more flexible.

In a study conducted by Kupčová et al., a total of 24 subjects were assigned to one of four groups ($n = 6$) based on whether they had a normal liver function or stable hepatic impairment defined as mild, moderate, or severe (Child–Pugh grades A, B, and C, respectively).[44] PK blood samples were obtained up to 120 hours after the dose, and fractionated urine samples were collected.[44] The ultra-long PK characteristics of insulin degludec were retained in people with hepatic impairment. The degree of hepatic impairment does not affect the total exposure to insulin degludec.[44]

Hepatic illness and insulin requirements have a complex association. As a result, insulin degludec (and, indeed, any insulin) treatment should be tailored to the individual's needs.[44] Based on results from the current experiment, a population PK model was used to simulate the PK profiles of insulin degludec to steady-state in participants with hepatic impairment.[44]

Insulin Glargine

There is no published evidence available for insulin glargine in people with CLD.

Prandial Insulins

Insulin Aspart

Insulin aspart is absorbed into the blood faster than HI following subcutaneous injection, resulting in a higher maximum concentration (C_{max}). This is because insulin aspart hexamers dissociate more quickly.[45]

Holmes et al. examined the effects of obesity, renal impairment, and hepatic impairment on the PK of insulin aspart.

Of 65 patients enrolled in the study, a total of 24 patients (males = 15; females = 9) with hepatic impairment (with or without ascites), BMI ≥19 but ≤38 kg/m^2, and fasting blood sugar <8.33 mmol/L were categorized by Child–Pugh score (Table 2).[45]

Hepatic impairment or BMI had no significant effects on PK parameters with respect to the Child–Pugh Score.[45] There was no clinically relevant effect of HI on the PK of insulin aspart in normal hepatic function or mild/moderate/severely compromised hepatic function.[45]

Insulin Lispro

Gentile et al. compared lispro, a fast-acting insulin analog, to regular human insulin (RHI) in people with T2DM and compensated CLD in a 12 + 12-week cross-over trial.[16] A total of 108 people with T2DM (with fasting blood glucose between 6.7 and 8.9 mmol/L and postprandial levels over 10 mmol/L during the last 3 months) and CLD (only Child–Pugh's score stage A or B) were randomly assigned to insulin lispro or RHI treatment. People with Child–Pugh score stage C were included in this study because of their catabolic status, increased insulin resistance, and low BMI.[16]

This study demonstrated that in people with compensated CLD and T2DM who did not respond to lifestyle changes, lispro was significantly more effective than RHI at improving glucose control and that glycemic fluctuations were higher under RHI than lispro. The insulin concentrations before and after a standard meal, the incremental area under concentration, and the glycemia are well-controlled. Lispro reduced early postprandial glucose levels and late postprandial hypoglycemia rates, suggesting that it is a potential therapeutic option for persons with T2DM and compensated CLD.[16]

Insulin Glulisine

There is no published evidence available for insulin glulisine in people with diabetes and CLD.

Premixed Insulins

There is no published evidence from clinical trials available for premixed insulins in CLD.

When a basal insulin analog is insufficient to maintain glycemic control, the clinicians may use one of two approaches (1) a basal-bolus approach, which includes separate bolus insulin injections but requires titration of two different insulin formulations, or (2) switch to premixed insulins, which provide better glycemic control than basal insulin, but may be associated with lower fasting plasma glucose and HbA1c levels.[46]

Coformulation of insulin degludec and insulin aspart (IDegAsp) was studied in the general population and people with hepatic impairment, and it was found that no interim control is achieved with the insulin aspart component, while the flat and stable control is achieved with insulin degludec which is the basal component of the coformulation.[44–46]

The IDegAsp has unique prandial as well as basal glucose-lowering actions in steady-state. It is both safe and effective in people with diabetes who have hepatic insufficiency. Because the PK of insulin degludec or insulin aspart is unaltered, this coformulation can be safely used in people with diabetes and hepatic impairment.[44–46]

Glycemic Markers and Glycemic Targets for People with CLD

Composite glycemic control indicators are recommended to bridge the gap between distinct glycemic control markers (Table 3).[17] The first challenge is to establish an accurate diagnosis and determine the disease severity.

Composite parameters are also available; however, they are more useful in theory than in practice.

There are very few guidelines for maintaining glycemic targets in people with CLD. Because most medicines are metabolized by the liver, pharmacological options for management, as well as concerns about hypoglycemia and malnutrition must be carefully considered. Individualized glycemic targets must be used to address these concerns. Composite parameters should be closely monitored because HbA1c values may be erroneously low.

Clinician's Expert Opinion

A clinician may face a variety of challenges when treating people with liver disease, particularly if there is insulin resistance triggered by a decrease in hepatocyte number, inflammation, or fibrosis. The two major issues to consider are (1) reduced insulin clearance by the liver and (2) hyperinsulinemia as a result of the systemic clearing process. Because there is a need to balance the risk of hyperglycemia, this form of classification is a very useful tool for the management of people with CLD who are on insulin therapy.

The Expert Panel and Methodology Followed

Based on clinical evidence from published literature, prescribing information on insulin preparations with dose modification recommendations, developed after due consideration of the PK/PD profile of insulins in hepatic impairment, and the clinical experience of the clinicians, clinicians including diabetologists and endocrinologists (henceforth experts) provided their opinion on the use of insulin regimen in people with CLD and diabetes.

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- Dr Shalini Jaggi, MBBS, Post Graduate Diploma in Endocrinology (Consultant

Table 2: Stages of CLD based on Child–Pugh Classification

Class	*Stages of chronic liver disease*	*Child–Pugh score*
A	Well-compensated disease	5–6
B	Significant functional compromise	7–9
C	Decompensated disease	10–15

Table 3: Glycemic control monitoring tools in patients with CLD and diabetes

HbA1c	HbA1c values in people with CLD are often deceptively low, and interpretation should be done with caution due to the risk of hemolysis, anemia, hypersplenism, and blood loss, as well as the effect of alcohol use. A lower diagnostic threshold is needed in people with CLD[15]
Glycated proteins	Most clinicians do not use glycated proteins (fructosamine and glycated albumin) very often, and they also do not interpret them very well. Glycated protein levels are affected by changes in protein metabolism and liver cirrhosis. Liver disease and dietary intake influence 1,5-anhydroglucitol
Self-monitoring of blood glucose (SMBG)	Frequent and repeated SMBG may reflect short-term glycemic control
Continuous glucose monitoring (CGM)	CGM is highly recommended in specific cases. CGM directs the treatment approach and insulin dosage adjustments[17]

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- Dr Ashok Kumar Das, MD, PhD (Consultant Endocrinologist, Pondicherry Institute of Medical Science, Puducherry, India).

To extract the required published data, a literature search was conducted using PubMed, which included randomized and non-randomized clinical trials, case reports, evidence-based reviews, epidemiological studies, expert opinion, recommended treatment guidelines, and regulatory acts.

On 26th November 2021, the preliminary findings were presented at the 15th National Insulin and Incretin Summit in Bengaluru, India. The Diabetes Research Society (Dia Aid) convened the summit, which was funded by Novo Nordisk in Bengaluru, India.

The Indian expert group reviewed the evidence available for basal, prandial, or premixed insulins for the treatment of people with diabetes and comorbid CLD (cirrhosis, NAFLD, liver failure, etc.). The Child–Pugh class A, B, or C were used to classify the stages of CLD for the proposed recommendation (Tables 2 and 4).

After extensive deliberations during the summit, the expert panel reviewed and developed the consensus document on optimal dose adjustments with antidiabetic drugs in people with T2DM and concomitant CLD. The experts' recommendations were consolidated and appraised to compile the final proposed consensus opinion on the use of insulin, appropriate doses, and titration in people with CLD.

Dosing and Titration of Insulins in CLD

For individuals with decompensated liver disease (Child–Pugh class C), insulin therapy should ideally start in a hospital setting.[6] According to the expert's recommendations, insulin dosages in each stage of CLD can be estimated using the following criteria based on body weight and CLD stage (Child–Pugh score) (Table 5).

Titration of Basal Insulins in CLD

Insulin detemir has not been thoroughly studied in CLD individuals. The efficacy of insulin detemir has only been evaluated in two people, therefore, there is little evidence, and it indicates that this insulin is less effective in attaining glycemic control in these individuals. There is no reported evidence of insulin glargine in CLD individuals.

Only insulin degludec was evaluated for its efficacy and tolerability profile in CLD individuals, as well as its PK/PD profile. Insulin degludec was studied in 24 patients who were classified as having CLD stages A, B, and C.[42] However, there is a need for large clinical trials with large sample sizes and extensive follow-up periods. The total daily dose should be reduced by 10–12% if the patient's nutritional status is good.

Dose reduction or long-acting insulin are not recommended for individuals with CLD class C because they will be in a semi-conscious or unconscious state or on dialysis, and even if long-acting insulin is given or the patient becomes mildly hypoglycemic. It will be difficult to manage unless the patient has live continuous glucose monitoring (CGM) to judge how much insulin is broken down, so it is preferable to use short-acting insulin with a 25 or 50% dose reduction. Basal insulin also prevents the breakdown of glycogen stored in the liver, which is a significant risk factor. Because there is no glycogen stored in a liver failure, long-acting insulin may not be as effective as it would be in a healthy individual or mildly liver-compromised state. Therefore, long-acting insulin should be avoided or used only when short-acting insulin fails to achieve glycemic control. Premix insulins should not be avoided, especially if the patient's condition has improved from class C to A.

Titration of Prandial Insulins in CLD

The prandial insulin dose can be reduced by 25% initially while the patient's glucose

Table 4: Child–Pugh score parameters

Parameters	*1 point*	*2 points*	*3 points*
Serum bilirubin total (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin (mg/dL)	>35	28–35	<28
International normalized ratio	<1.7	1.71–2.20	>2.20
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grades I–II (or suppressed with medication)	Grades III–IV (or refractory)

Child–Pugh A = 5–6 points; Child–Pugh B = 7–9 points; Child–Pugh C = 10 or more points.

Table 5: Dosing and titration of basal, prandial, and premix insulins in people with CLD and diabetes

Class	*Stages of chronic liver disease*	*Child–Pugh score*	*Total dose estimation of insulin in CLD*	*Titration of basal insulin in CLD*	*Titration of prandial insulin in CLD*	*Titration of premixed insulin in CLD*
Insulin (U/kg/day)						
A	Well-compensated disease	5–6	As in healthy individual	25–30% dose reduction	25–30% dose reduction	No change
B	Significant functional compromise	7–9	25–30% dose reduction	50% dose reduction	30–50% dose reduction with glucose monitoring	Consider biochemical parameters
C	Decompensated disease	10–15	Individualized	Not Recommended	Individualized	Avoid premix insulin for initiation
Preferred choice of insulin			–	Degludec (ultra-long PK properties are preserved)	Analogs	Analog mix or co-formulation

CLD, Chronic liver disease; PK, Pharmacokinetics; TDD, Total daily dose; U, Unit

Table 6: Glycemic targets [HbA1c (%)] and frequency of SMBG in people with CLD and diabetes

Stages of chronic liver disease			*HbA1c %*	*SMBG*
Class	*Parameters*	*Child–Pugh Score*		
A	Well-compensated disease	5–6	<7.5	2–3 times/day
B	Significant functional compromise	7–9	7.5–8.5	5–7 point profile/CGM
C	Hepatic encephalopathy	10–15	Individualize	5–7 point profile/CGM

CGM, Continuous glucose monitoring; HbA1c, Glycated hemoglobin; SMBG, Self-monitoring of blood glucose

profile is being monitored. The dose can be titrated based on the patient's postprandial glycemic expression and whether the patient's food intake is adequate with reference to Child–Pugh scores A and B categories.

Titration of Premixed Insulins in CLD

People with CLD in classes A and B can receive premixed insulin. It could be continued if the patient with decompensated disease (class C) is already on premixed insulin and his or her condition is under control without hypoglycemia. In these instances (individual in class C), titrating premixed insulins is challenging because the patient's appetite and general state may be constantly compromised and unstable.

Glycemic Targets and Blood Glucose Monitoring in CLD

The cause of low HbA1c values in the individual with CLD could be because of the reduced lifespan of all insulins, hypersplenism, as well as gastrointestinal fat loss, and gastrointestinal hemorrhage leading to acute blood loss. It is challenging since the values of serum fructosamine and HbA1c are influenced by serum albumin levels. Clinicians frequently use SMBG and CGM values (rather than HbA1c values) to determine whether a patient's socioeconomic status allows them to bear the costs, especially if the patient has hepatic encephalopathy and a slight change in INR. Following that, rather than focusing on HbA1c levels, frequent estimation and monitoring of liver function, albumin and glucose levels, coagulation markers, and the patient's mental health are performed.

The HbA1c target for a well-compensated individual should be no more than 7.5%, however, experts recommend a wide range of HbA1c targets for those with significant functional compromise, ranging from 7.5 to 8.5%.

The expert panel recommends the following glycemic targets and the frequency of SMBG for people with CLD who are on insulin therapy (Table 6).

Conclusions

Insulin therapy is widely recognized as the first-line treatment for hyperglycemia in people with CLD. Insulin is non-toxic to the liver and may be used at any stage of CLD. The risk of hypoglycemia is more likely to increase in people with decompensated CLD. Based on available evidence and deliberation by the experts, careful insulin selection with appropriate initial dosage and titration, individualized glycemic targets, and frequent glucose screening are recommended for optimal glycemic control without hypoglycemia in CLD.

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